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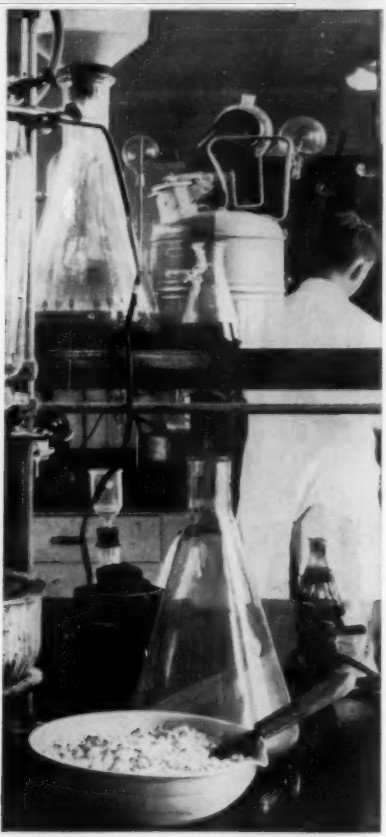

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AMERICAN JOURNAL OF PHARMACY

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OUR COVER

MR. JOSEPH M. BRANSKY

THE retirement of Mr. Joseph M. Branksy as Supervisor of District 3 of the Bureau of Narcotics might seem to many not knowing this stalwart public servant just a routine measure in the current stream of human affairs. Those who have known Joe Bransky as a friend and colleague would surely think otherwise and we are proud to have been his friend these many years. Mr. Bransky has served in the Bureau of Narcotics for forty-three years and has worked both in the United States and in the Far East. While in Japan on loan to the U. S. Army by the Treasury Department, he rendered invaluable service in restoring order in the distribution of narcotic drugs through legitimate channels and, through his "extracurricular" activities, helped in the formation of the Japanese Pharmaceutical Association for which he was awarded special honors by the Japanese government.

Mr. Bransky is himself a pharmacist, having been so trained at the University of Maryland where he also took some law courses in order to give him a better understanding of the field which he was to enter. As a pharmacist, Mr. Bransky always considered his relation with other pharmacists to be largely an educational one rather than that of a police officer, and it doubtlessly was this approach which made for him so many firm friends in so many parts of the United States. On the other hand, Mr. Bransky was not one to close his eyes to the deliberate and willful violation of the Harrison Act or its attendant regulations, and he was one of the men whom Commissioner Anslinger gave his complete confidence and trust. In viewing the career and life of Mr. Bransky, one cannot help but be impressed with the unique sense of personal dedication which he gave his public trust. Joe Bransky literally "lived his work" giving it every waking hour of every day of the year, and giving it, furthermore, a dedication which few public servants can match. In this day and age when a sense of personal responsibility is not too often observed, men such as Joe are the kind who can be pointed to as the ones who encourage respect for government and contribute to the willingness on the part of those so governed to give it their endorsement. Joseph Bransky was and is a loyal American citizen of that kind and quality which this country so desperately needs.

EDITORIAL

THE A. M. A. AND PROPRIETARY DRUGS

THE recent announcement by the A. M. A. to the effect that it intends to engage in a campaign to correct the excessive use of many over-the-counter proprietary drugs by the public is commendable. Since many of these products have become exploited by mass media of advertising, the public gradually has been led to consider these substances as in the same category as foods and beverages rather than for the dangerous, potentially toxic substances which they are. Many leaders in pharmacy have also decried the tremendous expansion in self-medication in the last decade as well as the continued efforts on the part of manufacturers to still further expand the availability of such products in retail outlets even by such mechanisms as vending machines and other entirely impersonal methods of distribution. It is also quite well-known that organized pharmacy in many states has attempted to regulate the sale and distribution of these proprietary preparations in such a way that their sale would have some little degree of professional supervision in the hope that some of the present abuses might be corrected. The proprietary interests, of course, immediately pointed the finger at such efforts as being motivated solely by economic interest which, while it may play some part as a motivating factor, is not the only force behind such moves. To say that it is, is to deny the existence of any professional motivation whatsoever in the realm of pharmaceutical practice. This, of course, is an utter lie which any objective examination will clearly establish. If anyone is motivated solely by economic interest and without regard for public welfare, it is some of those who manufacture and distribute these drug products using every trick known on Madison Avenue to encourage their promiscuous use. It is for this reason that they are sold in quantities far beyond their actual need and that which is in the interest of public health and welfare.

It is somewhat ironic that the American Medical Association has at this late date unleashed a public campaign to correct some of these abuses. In pharmacy's efforts to do so, it has had little or no

support from its medical colleagues. In fact, some physicians of repute have testified in defense of these manufacturers and their practices, much to the chagrin of pharmacists and with damaging results to pharmacy's efforts to bring some semblance of order out of chaos.

We in pharmacy welcome our medical brethren into the running battle which we have been having on this score and a battle which to date has been seemingly a losing one for both pharmacy and public health. If our two professions would give each other mutual support on this and other issues, each would find its efforts more effective in meeting its professional responsibilities and giving to the public that degree of guidance and protection which the public has a right to expect.

L. F. Tice

NEUROHORMONE-PHRENOTROPIC DRUG ACTIVITY CORRELATES

By Paul V. Buday *

RECENT neuroanatomical, neurophysiological, and neurochemical findings, encouraged by the development of a sundry potpourri of exotic drugs which seemingly modify learning, thought, and mood processes, have opened up a novel approach to the pharmacotherapy of mental disease.

A new pharmacologic discipline, neuropsychopharmacology, is the contemporary attempt to correlate mental aberrations, emotion, and behavioral patterns with disturbances in normal brain biochemistry. The large bulk of this research appears to be moving along two fronts. One concerns the investigation of substances which induce and simulate neurotic and psychotic states (psychotomimetics). The second involves the search for "brain chemicals" which can modulate these natural and artificial mental conditions.

Brain function and the psyche (Ego), although distinct entities, are in intimate contiguity and interdependence. Current psychopharmacologic concepts are based upon these relationships, i.e., a diminution, augmentation, facilitation, recruitment, etc., in the functional capacities and associative mechanisms of certain brain centers will be reflected in changes in the psyche. In fact, certain hypotheses propose that a cranial metabolic system exists which coincides with a functional neurophysiological system and a psychoanalytical behavioral mechanism (1). S. Freud once observed that "behind every psychoanalyst stands the man with the syringe" (2). Even in his time, Freud obviously foresaw the impending impact of chemicals on mentation and mood.

Albeit electrophysiology is indispensable for the study of how the phrenotropic agents act, one must eventually examine the cell and how its physiologic architecture is affected by chemicals, native or alien. The neurohormones primarily implicated in the neurochemistry of the body's signal system and in the *modus operandi* of the phrenotropic drugs thus far include: epinephrine (E) and norepinephrine (NE),

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the so-called "sympathins", dopamine, 5-hydroxytryptamine (serotonin, 5-HT), histamine, acetylcholine (Ach), gamma-aminobutyric acid (GABA), adrenochrome, and substance "P".

Involved intimately with these biogenic substances are the respective biocatalysts (enzymes) which synthesize or biotransform these psychochemicals. Generally, the neurohormones upon synthesis are stored, biologically inert, in some cytoplasmic structure unavailable to enzymatic catabolism. Upon release (e.g., neurosecretion), these transmitters become physiologically active and regulate nerve impulse transmission, combine with a cell receptor, e.g., a cell membrane protein, or affect other target sites. Thence, and within a minute fragment of time, a specific enzyme biotransforms the particular mediator to a less active or inert metabolite thus terminating the former's excitatory or inhibitory properties.

The brain distribution of the neurohormones is relatively well documentated. These data, in part, give the neurophysiologist and psychopharmacologist some rational basis for proposing or defining functions of these compounds and for postulating drug-action mechanisms.

The brain distribution of NE, a precursor of E, is asymmetric; highest levels are found in "primitive" brain areas, i.e., the hypothalamus, area postrema, medullary reticular formation (arousal-awareness center), and medial thalamus (3). Epinephrine also follows this repartition, but in lesser concentrations. The corpus striatum, an important link in the extrapyramidal system, contains the highest brain levels of dopamine (4). Here, however, only small quantities of NE are detected and it appears that brain sites (e.g., hypothalamus) rich in this substance are poor in dopamine (5). Serotonin, formed from 5-hydroxytryptophane through the agency of the corresponding decarboxylase, follows the localization of NE rather closely (6-8). Peripherally ubiquitous histamine is found in significant amounts only in the cerebellum and hypothalamus. Central histaminergic synapses, however, have not as yet been demonstrated (9). Acetylcholine, purported (10) to be synthesized from the naturally occurring amino alcohol, dimethylaminoethanol (11), has been identified particularly in the cerebral cortex, pons, basal ganglia, thalamus, and various brain nuclei (12, 13). It thus follows the distribution of brain 5-HT not unclosely. Manufactured solely in vertebrates by the action of l-glutamic acid decarboxylase on glutamic acid (14), GABA is

predominantly concentrated in the rhinencephalon ("visceral brain"), medulla, pons, and cortex (15). The elusive and labile indole amine oxidation product of E, adrenochrome, has been identified in erythrocytes and myocardial tissue (16). Still another naturally occurring product is substance "P", a biologically active polypeptide, found in the intestines and brain, especially in the basal ganglia, thalamus, hypothalamus (17, 18), area postrema, and spinal cord (19).

The functions attributed to these central occurring neurohumours have only been limited by the imagination of the active investigators in this discipline. This story probably began a short number of years ago when Hess (20) proposed that a subcortical brain system existed which was involved in the integration of autonomic, somatic, and psychic functions. This organization is said to be composed of two reciprocally antagonistic divisions, viz., the "ergotropic" and the "trophotropic" nervous systems. The former is concerned with arousal and an activated mental state, enhanced skeletal muscle tone, and augmented sympathetic activity. The latter involves sleep, apathy, and psychic depression, a deceased voluntary muscle tonus, and an increased parasympathetic activity (21).

As a consequence of a series of pathbreaking papers, Brodie and Shore (8, 22, 23) have postulated that free (active) 5-HT and NE serve as the chemical synaptic mediators for the trophotropic and ergotropic nervous systems respectively.

Epinephrine and NE (24), as well as 5-HT (25), are intercortical synaptic inhibitors and thus Marrazzi and Hart are of the opinion that certain mental disturbances result from an inbalance between serotoninergic and adrenergic inhibition and cholinergic facilitation in the more susceptible cerebral synapses.

Woolley and Shaw (26, 27) have proposed that some mental aberrations, including schizophrenia, are elicited by a metabolic deficiency of brain serotonin. These same workers have also discovered an unusual excitant action of 5-HT on cortical oligodendroglial ("nerve glue") cells. They hypothesize that this neurohormone serves to augment cerebral metabolic processes through this neurotonic effect (28).

The central implications of histamine are still obscure. Indirect incrimination of this enigmatic substance in mental reactions lies with the antihistaminics, many of which possess cogent effects on the central nervous system (CNS) and behavior. Histamine (and

methylated derivatives) are known to be substrates for the enzyme monoamine oxidase (MAO) (29), an enzyme involved in anti-depressant drug action. Histamine has also been given the role of a chemical mediator for peripheral pain impulses (30).

One prevailing doctrine (31) relegates Ach a synaptic transmitter role not only in the autonomic nervous system (ANS), but in the cerebrospinal axis as well. Because of its facilitating action on brain stem reticular formation synapses, Himwich and Rinaldi (32) theorize that elevated brain concentrations of Ach may serve an anti-schizophrenic purpose.

Still another central synaptic inhibitor is GABA, part of "Florey's factor". Purpura *et al.* (33) posit that this amino acid metabolite officiates as a transmitter substance, i.e., as an inactivator of synaptic depolarization and excitation. It has been suggested that it may play a role in neuro-excitability and brain abnormalities, e.g., epilepsy (14, 34). GABA might also underlie the nature of action of certain convulsive drugs (35).

Hoffer (16, 36) and his Canadian group have advanced the singular and imaginative hypothesis that adrenochrome, or dihydroxyindole products of aberrant E oxidation, because, among other reasons, of its close structural similarity to indole hallucinogens, e.g., lysergic acid diethylamide (LSD), is the cause of schizophrenia. This concept, although plausible, has not been consistently substantiated (37, 38).

Substance "P" has been proposed as a neuro-transmitter in the spinal cord (dorsal horns) (39), and as a "non-cholinergic" mediator in the ANS (40). It has been likened to a type of "physiologic tranquilizer" because of its central polysynaptic inhibitory characteristics (41).

The functional significance of the enzymes responsible for the innate biotransformation of the central mediating neurohormones is, as mentioned previously, a topic pregnant with implication and inference. The stimulation or depression of these degradating catalysts will directly cause a respective deficit or accumulation of their hormonal substrates in the CNS.

The pharmacodynamic actions of the "psychic energizers", or MOA inhibitors, probably best exemplify this relationship. MAO is widely distributed in the body tissues (mitochondria). Centrally, this enzyme is usually located where "true" cholinesterase enzyme

levels are low, viz., lenticular nucleus, hypothalamus, and pyramidal tracts (42). Formerly, as a consequence of initial drug mechanism studies, MAO *in vivo* and *in vitro*, was considered the enzyme primarily responsible for the metabolic conversion (deamination) of E (and NE), as well as 5-HT (43); more intensive work (44-46), however, has indicated that catechol-0-methyltransferase, MAO not withstanding, is the prime catabolizer, and relegates MAO the primary function of decomposing the relatively inert metanephrines and other 0-methylated catecholamine metabolites (47), and of biotransforming 5-HT to 5-hydroxyindoleacetic acid (48). The findings of Muscholl (49) that preferential tissue reactivities to MAO may be responsible for these disparate reports is well taken.

The definitive mode of action of the MAO inhibitors is still controversial. Their stimulating and alerting properties nevertheless appear to be related to their potent MAO or dopa-decarboxylase (50, 51) inhibitory effects, and hence, in any case, to elevated 5-HT and/or catecholamine brain levels.

Reserpine, a hypotensive and tranquilizing agent, impairs the ability of brain and other tissues to store (depletion reaction) 5-HT (52), NE (53, 54), and dopamine (55), and renders normal cell receptors, in some manner, refractory to the usual action of these mediators. These effects may explain the findings that reserpine inhibits the posterior hypothalamus, rendering it insensitive to signals from the reticular formation (32), and its ability to stimulate the trophotropic division with a subsequential enhancement of central parasympathetic irritability (21).

Chlorpromazine (and other phenothiazine tranquilizers) depress the hypothalamus-reticular activating system (32, 56), and block the ergotropic system causing a resultant diminution in central sympathetic discharge (21).

The psychic disorganizing activity of LSD still lacks intimate definition. It does seem to possess an action on the autonomic centers in the mesodiencephalic area, perhaps because of competitive antagonism with 5-HT (57).

In summary, a number of central neurohumours have been characterized and assigned functions. The influence of various psychoactive agents on histamine, GABA, adrenochrome, and substance "P" is poorly, if at all, known. The bulk of meaningful research points to the remaining chemical mediators as operative, and the

following scheme * is offered to recapitulate mechanisms of action of the psychic depressants and antidepressants:

Psychodynamic Activity	*Phrenotropic Drugs*
Excitors of ergotropic system (act via mimicking brain NE)	methylphenidate (Ritalin®), pipradrol (Meratran®), amphetamine, LSD, and imipramine (Tofranil®)
Ergotropic system depressants (act by antagonizing brain NE)	phenothiazine tranquilizers
Catecholamine and 5-HT metabolite inhibitors	MAO inhibitors
Brain NE and 5-HT depleting substances	reserpine (Serpasil®) and benzoquinolizines
Cholinergic stimulators (facilitate central synaptic transmission)	deanol (Deaner®)

Obviously the emphasis in neuropsychopharmacology has been on the role of centrally active neurohormones. Although space does not permit more than passing reference to the importance of vitamins, especially the B-complex family, in the etiology of mental illness, their paramount significance in intracellular enzyme systems and brain metabolism (58) cannot be stressed too cogently.

Unfortunately, no present neurochemical or psychopharmacologic finding is able to correlate neural function explicitly with motivation and emotional behavior. For example, Ostow (59) has called attention to the fact that the reticular activating system, although exerting a modulating influence on psychic activity, does not participate in any fashion in this complex phenomenon. Nevertheless, contemporary research in neuropsychopharmacology, if not divorced from basic psychologic tenets, should provide us with a fresh introspection on the "whys" and "hows" of behavior and mood (cf. ref. 60). Man's patience may be all that is wanting in attaining this goal.

* Adapted from Brodie, B. B. *et al.* (21).

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A REVIEW OF BIOFLAVONOIDS

By Eugene E. Vogin *

THE concept of "vitamin P" developed from the observation of Szent-Gyorgyi and his associates (1-3) that crude preparations of ascorbic acid obtained from natural sources were more effective in alleviating the capillary lesions and prolonging the life of scorbutic animals than was the purified vitamin. For several years following the isolation of ascorbic acid from adrenal tissue by Szent-Gyorgyi in 1928, he searched for a substance which might function as a co-enzyme with this vitamin. His attention was directed to the so-called benzopyrones (more specifically the flavones) and, in 1936, he succeeded in isolating a compound from lemons and red peppers which he termed "citrin". Although "citrin" was first thought to be a pure compound, having been isolated in crystalline form, it was subsequently found to be composed of three different, although related, substances: hesperidin, eriodictyol glucoside, and a quercitin-like substance (1-3). Since "citrin" appeared to be concerned with capillary permeability, Szent-Gyorgyi designated this substance as "vitamin P" (permeability). Due to the large variety of substances possessing "vitamin P" activity, and since these substances have been identified chemically as flavone derivatives, and because the status of these compounds as vitamins is by no means certain, they are generally designated by the more appropriate term, flavonoids or bioflavonoids.

The role of the capillary system in health and disease has often been stressed. However, the fact that abnormalities in the function of the capillary system are often the underlying factors in many chronic ailments is frequently overlooked and is sometimes a direct cause of death. Boyd (4) pointed out, "There was a tendency to pay exclusive attention to the heart and the blood vessels, and it was often forgotten that the sole function of the heart, the arteries, and the veins is to maintain an adequate rate of blood flow through the capillary beds. It is in the capillaries that the essential business of the circulatory system is carried on." A brief analysis of the factors which

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may affect capillary permeability and fragility is necessary before bioflavonoid activity can be properly considered.

The capillary wall consists of a single layer of endothelial cells which are bound together by so-called intercellular substance. The endothelial cells have a large nucleus of oval form with the plasma containing glycogen-like incorporations and a dispersed net of mitochondria. An outer tube surrounds the endothelium of the capillary. Nagel (5) stated that this outer tube consists of a network of argyrophil fibers of connective tissue origin and is filled with a delicate membrane which provides a continuous sheath to the endothelial wall. Attached to the connective tube, there are a number of cells known as "Rouget Cells." According to Ham (6), the role of the "Rouget Cells" as the contractile elements of the capillary is disputable.

It was formerly considered that non-protein substances simply passed through the spaces between adjacent endothelial cells of the capillary wall, but pores have been found to exist in the intercellular substance which serve as "selective seives." These pores are dispersed in intercellular space between the endothelial cells which form the capillary wall, in more or less regular order, and their contour is defined by so-called intercellular cement which gives some stability to the pores. Studies of this cement have shown that it can be modified or can disintegrate under special conditions. Chambers and Zweifach (7) demonstrated that, when there is a sufficient amount of calcium present in the plasma and when the pH of the plasma is neutral or nearly neutral, the capillary wall or, more exactly, the pores are almost impermeable to carbon particles. However, when the capillary is perfused with a calcium-free solution, capillary permeability is considerably increased. Aschoff and Koch (8) and Wohlbach and Howe (9) interpreted increased capillary fragility as a chemical modification in the intercellular cement. Dalldorf (10) expressed the opinion that the capillary fragility present in scurvy "is not pure vitamin C deficiency." In this connection, Puig-Muset (11) postulated that the intercellular cement of the capillary wall is "tanned" by the flavonoids and thus rendered less impermeable or almost impermeable to protein.

It appears that, under certain chemical conditions which might be present in some metabolic disturbances, the intercellular cement undergoes such changes that an increased capillary permeability and fragility may occur. To clarify the terms capillary fragility and capillary

permeability, the definitions of Sokoloff (12) and Danielli (13) may be cited. Capillary fragility is defined as a condition that will exist when chemical lesions in the capillary wall are apparent; whereas, capillary permeability is designated as "the volume of fluid filtered across the capillary membrane per unit of time." This latter definition has been further expanded to imply a temporary condition occurring as a result of neurogenic factors (14).

The exact role of flavonoid factors in the maintenance of capillary integrity has undergone extensive investigation, but has not been clearly elucidated, as yet. The micro-chemical investigations of Sokoloff and Redd (14) suggested the presence of bioflavonoid factors in the intercellular cement and, in the case of increased capillary permeability, these factors could no longer be detected. It is the purpose of this review to consider the many disease states in which bioflavonoids have been employed, and the various mechanisms which have been advanced to explain the activity possessed by the bioflavonoids.

To determine the effectiveness of the bioflavonoids in maintaining capillary integrity and reducing capillary fragility, many tests have been devised. Menkin (15) has offered an ingenious method for determining capillary fragility. He stated that the appearance of a foreign protein in blood serum would cause a temporary injury to the capillary wall and consequent increased capillary permeability. For the foreign protein, Menkin used an inflammatory exudate or a protein substance isolated from that exudate, termed leukotaxine. The method consisted of injecting either the exudate or leukotaxine into the cutaneous tissue of the abdomen of the rabbit, immediately followed by an intravenous injection of 10 to 15 ml. of a 1% trypan blue solution in saline. The dye rapidly accumulated in the areas of skin previously inoculated with exudate or leukotaxine, and induced a fairly homogenous staining of the affected tissue. Sokoloff and Redd (14) have used this method with considerable success for determining flavonoid activity on capillary permeability.

Ambrose and DeEds (16) using a modification of Menkin's technique were able to demonstrate that rutin decreases capillary permeability and fragility in rabbits. This method involved the intravenous injection of 2 ml. of a 1% trypan blue solution followed after a 5 minute interval by the topical application of chloroform. The time differential between the application of chloroform and the appearance

of the dye is noted. These investigators (16) offered this method as a means for the quantitative measurement of the activity of materials decreasing capillary permeability.

In 1942, Bacharach and associates (17) studied the effect of bioflavonoids on the tensile strength of capillary walls by measuring the negative pressure required to produce petechial hemorrhages in guinea pigs. For this procedure, a glass cup was pressed for one minute or more against the skin, and the pressure within the cup was reduced by a suction pump to a given degree of negative pressure as measured by a mercury manometer. The pressure at which the petechiae appeared was considered to represent the level of capillary fragility.

Ambrose and DeEds (16) found their results to be less consistent and definite with the use of negative pressure than with chloroform wheals. In this instance, they concluded that the fragility factor rather than the permeability factor was involved. Nevertheless, in most of their tests, there was a pronounced delay in the penetration of the dye, a fact which indicates that rutin reduces the increased permeability of the capillary wall subjected to an irritant.

Whether or not the flavonoid factors actively participate in the maintenance of normal activity of intercellular substances—essential for capillary integrity—remains open to question. There is some evidence that ascorbic acid participates in the formation and maintenance of the intercellular substance. However, there appears to be a close biological relationship between the bioflavonoids and ascorbic acid, and both substances are deemed essential in the maintenance of normal capillary integrity (18).

The possible mechanisms by which bioflavonoids maintain capillary integrity have been summarized by Martin (19) to include: (a) a direct effect on the capillaries; (b) a potentiation of the action of ascorbic acid; (c) inhibition of hyaluronidase; (d) inhibition of histamine, by direct antihistaminic action, by inhibition of histamine release, or by inhibition of histamine formation; (e) inhibition of epinephrine oxidation; and (f) an action on bleeding and coagulation time.

Szent-Gyorgyi (1) demonstrated the action of "citrin" on the capillaries and, in 1937, Bentsath and Szent-Gyorgyi (20) stated, "We have reported previously that certain flavonones ('vitamin P') greatly influenced symptoms of experimental scurvy. This latter con-

dition was interpreted as a mixed 'C and P avitaminosis'. At our request, our experiments have been repeated by several laboratories. The results were partly corroborative and partly negative. The reason for this discrepancy is now cleared up. 'Vitamin P' requires for its activity the presence of traces of ascorbic acid. In the entire absence of ascorbic acid, 'vitamin P' is inactive."

Since that time, a considerable amount of evidence has been adduced to support the concept of a relationship between the flavonoids and ascorbic acid. Parrot and Cotereau (21), in 1946, and Gero (22), in 1947, showed that flavonoids protected ascorbic acid against oxidation *in vitro*. The *in vivo* correlation of these results has been demonstrated by both Gabe *et al.* (23) and Parrot *et al.* (24). It was further demonstrated by Parrot and Cotereau (25) that ascorbic acid exercised a similar protective effect on bioflavonoids. To establish this concept of ascorbic acid protection, these investigators (23-25) used ascorbutic guinea pigs.

In a substantiation of the *in vivo* relationship between ascorbic acid and flavonoids, Bhagvat (26) showed that supplementation of the diet of guinea pigs with hesperidin and ascorbic acid caused a greater increase in growth rate than occurred when ascorbic acid was given alone. Lecoq *et al.* (27) showed that flavonoids fed to guinea pigs on a scorbutogenic diet retarded the appearance of the symptoms of scurvy. In rats, flavonoids prevented the transient neuromuscular disturbances which occur with an ascorbic acid-free diet.

Selsman and Horoschak (28), after treating humans afflicted with spontaneous ecchymosis or purpura, suggested that ascorbic acid was of importance in maintaining the integrity of the capillary intercellular cement substance and that the flavonoids serve as a catalyst in a reaction combining ascorbic acid with a protein fraction to form this intercellular substance. While this work indicated that flavonoid factors could to some extent replace ascorbic acid, other reports (23, 24) showed that the converse was not true. Gabe *et al.* (23) found that the changes produced in guinea pigs on a bioflavonoid-free diet, which were similar to those obtained in scurvy, could not be prevented by ascorbic acid. The capillary fragility associated with "avitaminosis P" likewise could not be prevented by ascorbic acid (24). To the contrary, Fabianek and coworkers (29, 30) indicated that no flavonoid factor is necessary to prevent vascular fragility in the guinea pig, but that only ascorbic acid is required to maintain capillary integrity.

Duran-Reynals (31) suggested that the spreading factor, hyaluronidase, caused an increased capillary fragility by affecting the intercellular cement. On this basis, Beiler and Martin (32) postulated that this enzyme was involved in the maintenance of normal capillary integrity, and that the activity of the bioflavonoid compounds might be due to an effect on hyaluronidase. They found that the flavonoids, hesperidin and hesperidin methyl chalcone, alone had no effect on hyaluronidase *in vitro* but, when combined with ascorbic acid, they exerted a marked inhibitory action on the enzyme. According to these investigators, the inhibitory effect appeared to be due to a two-fold action: (a) a direct inhibition of hyaluronidase, and (b) a potentiation of the flavonoid action. Martin (19) using the technique of Ambrose and DeEds (16) reported this synergism between the flavonoids and ascorbic acid could also be demonstrated *in vivo*.

Since 1939, many investigators (33-39) have demonstrated bioflavonoid protection against histamine and anaphylactic shock. Hiramatsu (33) found that guinea pigs were protected against anaphylactic shock by large doses of hesperidin. Parrot and Richet (34) showed that scorbutogenic diets enhanced histamine toxicity in guinea pigs and that this enhancement of toxicity was prevented by catechin epimers. Wilson *et al.* (35), in 1947, reported that pre-treatment with rutin resulted in slight, though definite, protection of guinea pigs against the lethal effect of histamine. In 1951, Wilson, Booth, and DeEds (36) confirmed the protective action of rutin against histamine and stated, "The failure of certain other investigators (40-43) to substantiate this finding may have been due to excessive histamine dosage or the use of inadequately standardized animals." Wilson *et al.* (36) indicated that the protection afforded by the bioflavonoids is slight and is of theoretical, rather than clinical, interest. Rossi and coworkers (38) have reported the probable existence of synergism between ascorbic acid and hesperidin in the prevention of histamine-induced gastric mucosal damage in the guinea pig.

The mechanism of the antianaphylactic action of hesperidin and other flavonoid compounds has received considerable attention. Ungar (44) postulated that compounds of this type, particularly hesperidin methyl chalcone and epimerized D-catechin, inhibit release of histamine from blood cells. Martin *et al.* (45) found that flavonoids were effective inhibitors of histidine decarboxylase *in vitro*, and postulated that the antianaphylactic effect of these compounds is due

to the prevention of histamine formation. These investigators also showed ascorbic acid to be synergistic with the flavonoids in this respect.

Although contradictory reports (40-43) have appeared in the literature, considerable evidence suggests that bioflavonoids have an effect on histamine and histamine-like substances in the body. The flavonoid substances appear to have the ability to reduce the effects of endogenously produced, as well as exogenously administered, histamine, including its attendant increases in capillary permeability and fragility.

Assuming that the property of controlling capillary permeability could be attributed to an effect on the tonus of the pre-capillary vessels and that this effect could be manifested through the intervention of sympathin, Lavollay and Neumann (46) sought evidence of preservation of sympathin by the bioflavonoids. Purified extracts of oranges strongly inhibited the oxidation of epinephrine *in vitro*. Various flavonoids prolonged the action of epinephrine on the isolated guinea pig intestine and seminal vesicle. In the dog, a preliminary injection of quercitin prolonged the effect of epinephrine and prevented symptoms of shock following injection of peptone. In additional reports, Lavollay (47-49) confirmed his earlier findings and asserted that the major function of the flavonoids was that of an epinephrine antoxidant. He interpreted the decrease in capillary fragility following flavonoid administration as attributable to retardation of the oxidation of epinephrine.

The epinephrine "sparing" action of rutin was studied by Wilson *et al.* (35) who found a definite prolongation of the effect of epinephrine on the isolated guinea pig colon following addition of rutin to the fluid bathing the intestinal strip. Clark and Geissman (50) developed a method of assay based on the ability of the flavonoids to prolong the effects of epinephrine upon excised mammalian smooth muscle and to inhibit the formation of adrenochrome from epinephrine. Clark also found that many compounds, cited by the French workers (46-49) as having a marked effect on capillary fragility, were feebly active or inert in their tests. Clark and Geissman (50) arrived at the conclusion that the ortho-hydroxy groupings of the compound must be free in order to exert high activity in this respect. Hughes and Parkes (51) investigated the activity of several flavonoid compounds in guinea pigs subjected to "avitaminosis P" but receiving ascorbic

acid. Among eight chalcones effective in decreasing abnormal capillary fragility, only one contained the ortho-hydroxy phenolic structure postulated as being necessary for the retardation of epinephrine oxidation.

The antoxidant theory has been criticized by Sokoloff and Redd (14) in these terms, "The leading idea in Lavollay's work is that 'vitamin P' factors delay oxidation of adrenaline and that their usefulness as far as capillary permeability is concerned is ended. In other words, 'vitamin P' factors have no direct effect upon either the capillary wall or capillary permeability. Not only have they not proved that adrenaline maintains capillary tone; not only were they unable to demonstrate that adrenaline increases capillary permeability, but they have offered an insufficient evidence in defense of their basic viewpoint about the delaying action of 'vitamin P' on oxidation of adrenalin. It is true that Parrot and Cotereau have proved that 'vitamin P' factors delay *in vitro* oxidation of ascorbic acid and adrenaline. But no evidence has been offered by them so far that 'vitamin P' factors act in the same manner *in vivo* . . . There is not sufficient evidence available as to the connection between the vasoconstrictive effect of adrenaline upon blood vessels and the decrease of capillary fragility."

In addition to their actions on the vascular system, there is evidence to indicate that bioflavonoids may have an effect on blood itself. Several investigators (44, 52, 53) have reported that flavonoid compounds cause a decrease in bleeding time in guinea pigs and normal white rats. Plungian and associates (53) measured the coagulation time. Blood from white rats was collected in a capillary tube and rotated until coagulation occurred. In this experiment, the animals had been fed rutin, dicumarol and bile salts, either alone or in various combinations. The results indicated that the coagulation time was shortened by both rutin and bile salts, and the effect was additive when the two were given together. Dicumarol caused a lengthening of coagulation time, but this was largely prevented by the concomitant administration of rutin.

Martin and Swayne (54) measured prothrombin time of blood obtained from rats and found that certain flavonoids counteracted the effect of dicumarol on the prothrombin time. Balducci (55) found that bioflavonoids exerted a protective action against dicumarol intoxication in rabbits. Various other investigators (56-59) have administered both dicumarol and rutin to persons requiring anticoagu-

lant therapy. Matis *et al.* (59) stated, "The administration of rutin was justified in the course of anticoagulant therapy with dicumarol to prevent capillary damage, especially in persons with hypertension, diabetes, arteriosclerosis, and in the very old." In contrast, Bourgain and associates (60), in a study of the action of phosphorylated hesperidin on blood coagulation in rabbits, demonstrated a prolonged plasma recalcification time and an increased antithrombin activity when the compound was given intravenously. Neither of these effects was evident after oral administration. The action of phosphorylated hesperidin intravenously may be due to an interference either with the activation of the fibrinogen molecules or with the polymerization of activated fibrinogen molecules. The authors (60) stated that perhaps both mechanisms were involved.

In addition to these possible modes of action of the bioflavonoids, several other mechanisms have also been advanced. Bartlett (61) reported that the flavonoid 2,3,4-trihydroxychalcone inhibits rat liver succinoxidase *in vitro*. He postulated that the inhibition was due to the quinone-forming properties of the flavonoids. Beiler and co-workers (62) studying the *in vitro* inhibition of choline acetylase came to essentially similar conclusions.

Richards (63) and Richards and Kueter (64) found that the toxicities of intramuscularly or subcutaneously injected epinephrine and procaine were increased by injecting sodium bisulfite with these agents. The bisulfite increases capillary permeability and therefore accelerates the rate of absorption. These workers have shown that rutin has a prophylactic effect on bisulfite induced capillary permeability. Haley and Rhoades (65) used the procaine-bisulfite method (63, 64) to evaluate flavonoid compounds for their ability to modify capillary permeability. Male albino mice were injected intravenously with varying doses (5-250 mg./Kg.) of test compounds ten minutes prior to the intramuscular injection of 500 mg./Kg. of aqueous procaine containing 0.1% sodium bisulfite. The protection obtained with the flavonoids against the mortality and convulsions of procaine-bisulfite administration was believed due to the flavonoids indirectly acting as vasoconstrictors. These authors (65) proposed that the flavonoid compounds prevent relaxation of precapillary sphincters through inhibition of the enzymatic conversion of adenosine diphosphate to adenosine triphosphate which is essential for muscular relaxation. Closure of the precapillary sphincters results in a preferential

shunting of the blood flow into larger vessels thus by-passing the capillary bed and decreasing the interchange of materials between the circulating blood and the cells in the area.

Salgado and Green (66) determined the anti-inflammatory effects of several bioflavonoids in both normal and adrenalectomized rats. Using the granuloma pouch technique of Selye (67, 68), an injection of 25 ml. of air was made under the skin of rats anesthetized with ether followed by 1 ml. of a 1% solution of croton oil in corn oil. Drug treatment was started immediately and continued for 10 to 12 days. The bioflavonoids were assayed on the basis of their ability to produce a significant decrease in the amount of inflammatory exudate formed within the pouch. The results indicated that, as a class, the bioflavonoids possess anti-inflammatory activity when given parenterally. That anti-inflammatory activity was a property of the flavonoid nucleus itself was indicated by the relatively high activity of the pure substances, and the lower and less constant effects of the complexes and mixtures of flavonoids. As a result of studies in adrenalectomized animals, Salgado and Green (66) further stated that the anti-inflammatory activity was not dependent on the presence of an intact pituitary-adrenal axis. In contrast, Masri and DeEds (69) have suggested that the physiological effects of the bioflavonoids were mediated, at least in part, through an action on the pituitary-adrenal axis. Pending further investigation, this question remains unresolved.

Menkin (70) studied the anti-inflammatory activity of some water-soluble bioflavonoids. Using the method previously described (15), Menkin obtained inflammatory exudates from dogs previously injected with turpentine. These exudates, admixed with the bioflavonoids, were injected subcutaneously in rabbits. This was followed by an intravenous injection of trypan blue. The extent of accumulation of the indicator dye in injected skin areas was considered as the degree of inflammatory response. The results of this investigation indicated that the water-soluble bioflavonoid compounds tested repressed both the increased capillary permeability and the emigration of leukocytes induced by an injection of either inflammatory exudate or its contained leukotaxine, irrespective of pH. In comparison to either cortisone or corticotropin, to which they were compared, these bioflavonoid compounds appeared to exert an anti-inflammatory action over a larger pH range of exudates.

Utilizing frostbite in rats, Fuhrman (71) noted that flavonoids appeared to prevent extensive vascular occlusion. This may be due to potentiation of the constrictor action of epinephrine, or other endogenous sympathomimetic substances, on the metarterioles and precapillary sphincters with consequent reduction of the hydrostatic pressure in the capillaries. Reduction in the rate of passage of fluid outward through the capillary walls would result. Such rapid loss of fluid through the walls of the injured vessels appears to be one of the factors contributing to the development of stasis. Fuhrman was also able to demonstrate antagonism by the flavonoids of the action of a vasodepressor material resembling ferritin.

Living cells may be damaged or destroyed by a variety of physical agents, including heat, cold, ionizing radiation, etc. Due to world events, a large literature has become manifest concerning radiation toxicity and methods of minimizing the health hazards involved. Several studies indicate that bioflavonoids may decrease irradiation toxicity. Of the six possible phases of radiation toxicity expounded by Griffith *et al.* (72), the phase associated with bioflavonoid activity is the one concerned with capillary strength. These workers denoted this phase as, "A change in capillary strength, presumably due to an effect on the endothelial cells of the capillaries, and perhaps on adjacent cells and intercellular substance. It is our belief that rutin is effective in correcting this factor of increased capillary fragility and may be effective in this phase only."

Griffith *et al.* (73) studied the effect of rutin on localized radiation injury. Rats were subjected to a large dose of X-irradiation confined to one leg and immediately thereafter a rutin pellet of 20 mg. was implanted subcutaneously in half of the animals. Pellet implantation was repeated every third day. Periodic examinations disclosed that half of the rutin treated animals recovered in 21 to 25 days, and all had recovered by the 35th. day. In the control group, only 1 out of 26 had recovered in 21 to 25 days and, in 35 days, only 14 more animals showed complete recovery. The same investigators (74) also demonstrated that alpha radiation localized to the peritoneal cavity caused an increase in capillary fragility. Radiation was accomplished by injecting radon ointment into the peritoneal cavity of the rat. Increased capillary fragility was measured by the number of petechiae evidenced after applying pressure to the peritoneum. The

data (73, 74) indicated that rutin assisted in recovery from local irradiation injury.

Cohen and Cohen (75, 76) measured the increase in the median lethal dose (M. L. D.) afforded by rutin both before and after rats were exposed to whole body irradiation. While the M. L. D. was raised from 650 roentgen in the control animals to 750 roentgen in the treated animals, the difference cannot be considered as significant, but does tend to confirm the reported slight protective action of the flavonoids in totally irradiated animals. In regional irradiation, however, the M. L. D. in the rutin-treated animals was 3,200 roentgen, a value 45 per cent greater than in the control animals. These authors (75) also investigated the clinical use of rutin as an adjunct to radiotherapy involving the liver, pancreas, or stomach. Based on 7 cases, they showed that the clinical effect of premedication with rutin as an adjunct to radiotherapy was threefold: (a) the complete absence of any of the subjective or objective symptoms of radiation sickness; (b) prevention of the acute lethal action (tissue necrosis) or the hemorrhagic diathesis, and (c) a diminished skin reaction, usually little more than a mild erythema. On the other hand, rutin did not prevent the onset of the other aspects of post-irradiation syndrome; namely, leucopenia with infection, anemia, etc.

Rekers and Field (77) administered total body X-irradiation to fifty dogs, half of which were maintained on rutin therapy. Sixteen of the untreated dogs died between the 13th. and 30th. day; whereas, only three of the treated dogs succumbed in that same time interval. In the treated dogs that survived, rutin seemed to prevent the appearance of hemorrhagic lesions. In other similar experiments (78, 79), these workers concluded that the following flavonoids were also effective in lowering the mortality following whole body irradiation: hesperidin, epimerized D-catechin, homoeriodictyol, and morin. Clark and associates (80) determined the effectiveness of calcium flavonate in reducing the lethality of total body irradiation in guinea pigs. They found that the treated group had a mortality rate of 35 per cent as compared to 65 per cent in the control group. Sokoloff *et al.* (81-83), using a flavonoid product of citrus origin, were able to demonstrate a reduction in mortality following whole body irradiation in rats.

Cronkite *et al.* (84), using rutin, failed to decrease the mortality of acute ionizing radiation illness in mice. In the opinion of Griffith and associates (72), this failure of rutin to provide protection was

due to the *ad lib.* ingestion of the drug mixed with the diet. The sickest animals consumed little or nothing and, as a consequence, received little or none of the medicament. Haley and Mann (85) stated that they have shown "that rutin, hesperidin, hesperidin methyl chalcone, and naringen were ineffective in modifying roentgen ray irradiation lethality in guinea pigs."

The possible role of flavonoid therapy following whole body or "atomic" irradiation has been summarized by Griffith *et al.* (72), ". . . irradiation, at least in certain animal species probably including man, is characterized by an increase in capillary fragility . . . rutin can favorably influence this change in fragility, at least locally and may influence mortality . . . It seems logical to us to attempt to correct any abnormal effect produced by the irradiation, even if that effect by itself has not been shown to contribute appreciably to mortality."

Ershoff (86) found that flavonoids can significantly affect the response of immature rats fed purified rations containing either excessive or suboptimal amounts of vitamin A. When these animals were fed flavonoid-free diets containing massive but relatively nontoxic doses of vitamin A, supplements of various flavonoid compounds resulted in a striking accentuation of the symptoms hypervitaminosis A. These results suggested that the flavonoids may have promoted an increased absorption and/or utilization of vitamin A. These findings also indicated that flavonoids may play an important role in the treatment of vitamin A deficiency states, not only those arising from deficient intake of the vitamin, but also those resulting from impaired utilization or absorption of vitamin A.

Several investigators (87-90) have studied the effectiveness of bioflavonoids in counteracting the capillary damage and other toxic manifestations resulting from arsenical therapy. Horne and Scarborough (88) reported ten cases developing either toxic erythema, purpura, or dermatitis following anti-syphilitic therapy. All showed a low capillary resistance on the basis of the amount of negative pressure required to elicit the first petechial break. In two of these cases, the administration of hesperidin resulted in an increase in capillary resistance; whereas, ascorbic acid given alone in one case was ineffective. Scarborough and Stewart (87) reported that capillary resistance lowered as a result of treatment with arsenic and bismuth was raised by the administration of hesperidin. Goldstein *et al.* (89) studied the

histologic lesions produced in the brains of rabbits given toxic doses of mepharsen. Their findings suggested that the chief lesion was an increase in capillary permeability, and that hesperidin methyl chalcone produced a fourfold reduction in mortality.

With the development of newer antisyphilitic therapy, the use of arsenicals has markedly diminished. However, the generalization appears to remain applicable that certain drugs, whose toxicity depends upon the production of capillary damage, may be made less toxic by adjuvant therapy with bioflavonoids (72).

Call and Patterson (91) have been able to show that both ephedrine and epinephrine toxicity in rats can be reduced by pretreatment with various flavonoid compounds. This protective action of flavonoids is thought to be due to a reduction of the rate of absorption of the epinephrine, based on a decrease in capillary blood flow due to precapillary sphincter constriction, a reduction in the permeability of the capillaries, or a change in the permeability of individual cells.

There are several disorders in which unduly low capillary resistance is encountered, and among these is essential hypertension. In eighteen of twenty-one hypertensive patients, Weismann (92) observed increased capillary fragility. Schweppe *et al.* (93) reported similar observations in a group of forty-four hypertensive patients.

In clinical studies, the most prominent tests used in the evaluation of capillary fragility in hypertensive individuals were the Gothlin Infradiastolic Pressure Test (94) and its various modifications (95, 96).

Griffith and associates (95, 97, 98) performed several studies of capillary fragility in hypertensive states utilizing the Griffith and Lindauer Modification of the Gothlin test. In one study (95), it was concluded that hypertensive patients manifesting increased capillary fragility were especially prone to apoplexy, retinal hemorrhage, and death. These investigators concluded that flavonoid therapy is of definite value in correcting the increased capillary fragility associated with hypertension. Barishaw (99), using a method similar to Griffith's (95), and Selsman and Horoschak (28), using a modified Wright-Lilienfeld Positive Pressure Test (96), largely substantiated the work of Griffith and his associates.

Bacharach and Scarborough (100), however, did not succeed in confirming the observations of the above authors. They stated, "As to

the action of rutin in increasing the capillary resistance of hypertensive patients, our experience is that either an enormous quantity or a very prolonged administration is necessary before any demonstrable effect is obtained. We have, in fact, not yet succeeded in restoring to normal levels the low capillary resistance in any hypertensive patient by means of rutin."

Sokoloff and Redd (101) presented a critical evaluation of flavonoid therapy in hypertension. They stated that, since the experimental data concerning the factors of 'vitamin P' indicated that only a slight and temporary vasodilation might occur, one could hardly expect a direct action of the bioflavonoids on hypertension. It may be assumed, however, that a prolonged treatment with this 'vitamin' might gradually improve the functioning of the capillary system and, thus, indirectly exert some effect upon hypertension. In other words, the 'vitamin P' therapy should be considered only as an adjuvant to other medications used in the treatment of hypertension.

In a series of clinical investigations, Warter and his associates (102, 103) found that abnormal capillary fragility prevails in patients with rheumatoid arthritis, and hesperidin and ascorbic acid act synergistically to restore capillary integrity to normal. These results were verified by Sokoloff *et al.* (104) who considered bioflavonoids useful adjuncts in the therapy of rheumatoid arthritis. Rinehart (105, 106) and Shnir (107) have treated rheumatic fever patients with flavonoids and ascorbic acid. Benefit was claimed in all patients as manifested by control of fever and of cutaneous, visceral, and articular symptoms; reduction of the erythrocyte sedimentation rate; and stabilization or disappearance of clinical, roentgenologic, and electrocardiographic evidence of cardiac disease.

Because diabetic retinopathy is predominantly of a hemorrhagic nature, many clinicians have investigated the value of flavonoids in alleviating or correcting this pathologic state. Griffith *et al.* (72) have presented a comprehensive review of this work, and are of the same opinion as Brickley and his associates (108). The conclusion reached by these authors (72, 108) was that flavonoids do not offer any objective evidence indicating their use to be of value in the therapy of diabetic retinopathy.

Since the discovery of "citrin" (1-3), the bioflavonoids have been used in a large variety of clinical conditions. Willaman (109),

Griffith and associates (72), Horoschak (110), and Sokoloff *et al.* (101, 111) have reviewed a comprehensive literature pertaining to the therapeutic uses of bioflavonoids. The opinion fostered by these authors appears to be that bioflavonoids are of potential value in treating almost any disease state, especially if that disease is associated with increased capillary fragility and permeability. As an example, several workers (112-116) have reported that flavonoids, either alone or in combination with ascorbic acid, can abort the development and relieve the symptoms of the common cold. However, the studies of Tebrock *et al.* (117) and Franz *et al.* (118), representing probably the most definitive clinical reports in the flavonoid literature, were in complete disagreement with these findings. These workers (117, 118) conducted a double blind study of the effects of placebos, flavonoid with ascorbic acid, flavonoid alone, and ascorbic acid alone, in combination with a standard palliative preparation on colds occurring in nearly 2000 persons. In the opinion of the investigators, there was a singular lack of effect of both flavonoids and ascorbic acid in altering the course of the common cold. In no instance did apparent differences reach the 1% level of significance and, in most cases, simple inspection of the data was sufficient to deny signifiance.

This controversy regarding the therapeutic value of flavonoids in treating the common cold is not an isolated example. Martin (119) has generalized that supplementary therapy with flavonoids is of value in virtually all disease states and specific in action with respect to some. On the other hand, the American Medical Association Council on Pharmacy and Chemistry have published two reports (120, 121) which stated, ". . . the flavonoids are of little or no value in the treatment of disease."

This incongruity in regard to the clinical value of the bioflavonoids has been explained by Pearson (122). He stated, "The effects of flavonoids on such clinical entities as hypertension, diabetes, etc. have been studied. It is not possible to reach valid conclusion as to the efficacy of flavonoid treatment in these conditions because of (a) general unreliability of the techniques employed, (b) the absence of double blind placebo controls, and (c) the spontaneous remissions that are known to occur. Although it is admittedly difficult to obtain ideal experimental conditions in clinical situations, the therapeutic studies of the flavonoids seem to suffer peculiarly from lack of proper design."

In the view of many investigators, the bioflavonoids are of potential therapeutic value in those states involving either increased capillary fragility or capillary permeability. Of the possible modes of action of the flavonoids, those receiving most attention include: (a) direct effect on the capillaries, (b) inhibition of histamine, (c) inhibition of hyaluronidase, (d) potentiation of ascorbic acid, (e) inhibition of epinephrine oxidation, and (f) action on bleeding and coagulation time. In the multitudinous clinical conditions in which they have been employed, the bioflavonoids have often been found to be of value, but it must be remembered that much of the clinical work has been performed without adequate control and that many discrepancies exist.

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CARBOPOL 934 AS EPHEDRINE SULFATE JELLY BASE

By William B. Swafford *

EPHEDRINE SULFATE JELLY has long appeared as an official preparation in the *National Formulary*. Since its appearance, there has been no major change in its formula. The first supplement to NF VII permitted the omission of dwarf pine needle oil. Sodium phosphate is authorized as a stabilizer in the manufacture of the official formula (1).

In a study of this preparation, Fiedler and Lee (2) attempted to find a suitable formula for this preparation. Their study was based on the many objections that have been made to this preparation. Among these objections are: the product is thin and lacks the consistency of jelly; it is readily susceptible to mold growth; the official procedure requires that the formula mixture be allowed to macerate for one week, then strained before being completed for use. It was also pointed out that tragacanth jellies vary in viscosity with the quality of the gum used (3). This study has been directed toward the use of Carbopol 934 [1] as a base for Ephedrine Sulfate Jelly with the objective of improving both the formula and the procedure of the official formula.

Carbopol is a new synthetic designed to meet the need for a gel-forming material which is not subject to hydrolysis or polymeric degradation due to bacterial or fungal attack (4). It is a finely divided, free-flowing acid polymer. The white powder readily disperses in water to yield an acidic solution of low viscosity. When this solution is neutralized with an appropriate alkaline substance, the solution is transformed into a clear, stable gel (4). In this study, it is believed that the objections listed above concerning the official Ephedrine Sulfate Jelly have been overcome. In the final formula, a preparation having the consistency of jelly, no mold growth or deterioration of other kind has been noted in a fourteen month shelf test, and this preparation may be prepared immediately, there being no waiting period for maceration, etc.

* Assistant Professor of Pharmacy, College of Pharmacy, University of Tennessee.

[1] Courtesy of B. F. Goodrich Chemical Company, Cleveland, Ohio.

This formula was prepared using a mucilage of Carbopol 934 containing triethanolamine as the neutralizing agent. It was found that 2% Carbopol 934 made a suitable gel for this preparation. To prepare the mucilage and subsequently the jelly itself, the Carbopol 934 was slowly dispersed in water in which the ephedrine sulfate had previously been dissolved.

The amount of triethanolamine determined to properly neutralize this preparation of Carbopol 934 was 1.65 per cent. This was added to the Carbopol 934 mixture slowly with stirring. A smooth, viscous gel resulted. Into this gel, the oils were added with stirring.

The formula adjudged to be most satisfactory was:

Ephedrine Sulfate	10.00 Gm.
Methyl Salicylate	0.10 ml.
Eucalyptol	1.00 ml.
Dwarf Pine Needle Oil	0.10 ml.
Carbopol 934	20.00 Gm.
Triethanolamine	16.50 ml.
Distilled Water qs ad Approximately	1000.00 Gm.

Summary

Carbopol 934 is a synthetic hydrophilic gum which is capable of producing a gel for use as a base for Ephedrine Sulfate Jelly.

Triethanolamine was used to neutralize the acidic nature of the polymer in mucilage formation.

Ephedrine Sulfate Jelly may be extemporaneously prepared by this method with no waiting period.

Ephedrine Sulfate Jelly prepared with the use of this gum was observed to spread smoothly and to maintain its stability over a fourteen month shelf test period.

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SELECTED ABSTRACT

The Use of Guanethidine in the Treatment of Hypertension. Dollery, C. T., Emslie-Smith, D., and Milne, M. D. *The Lancet* No. 7147:381 (1960). A group of 80 patients with severe hypertensive disease were treated with guanethidine. The dosage employed ranged from 10 to 750 mg. a day, but most patients were stabilized on a dose of 30 to 120 mg. a day. Because of the severity of their disease, most patients were hospitalized during stabilization.

The authors reported that only ten per cent of the patients failed to respond to treatment. There was no apparent difference in the response of patients with renal and essential hypertension. In comparison with a series of patients previously reported who had been treated with bretylium tosylate, it was found that those treated with guanethidine did not become resistant to the drug and that the hypotension was less variable. Both of these drugs cause no parasympathetic blockage and, thus, patients are spared the discomforts of constipation, impotence, dryness of the mouth, and iridoplegia. However, guanethidine therapy must be given under strict supervision. It was found that the reduction in blood pressure was only effective when the patient was upright and the pressure while lying down often returned to high levels. It was also found that there was often a severe fall in blood pressure immediately following exercise. This may severely handicap the control of blood pressure in patients engaged in manual work. Guanethidine was also found to have a prolonged effect. One dose a day was sufficient to control the hypertension in most patients. Some patients showed a fall in blood pressure upon standing for as long as 4 days after the last dose. Although frequency of dosage is, therefore, less, this prolonged effect did not allow for the fine adjustments that were sometimes needed to counteract diurnal variations in pressure.

The main side effects from guanethidine were diarrhea and bradycardia, but neither interfered greatly with treatment.

Using chemical and radioactive-tracer techniques, it was found that the absorption of guanethidine from the gut was incomplete and that excretion in urine and feces was prolonged. Concentration of the drug was mainly intracellular, being highest in the kidney. It was excreted in the urine both as unchanged guanethidine and as three closely related metabolites.

BOOK REVIEWS

Biochemical Preparations, Volume 7. Henry A. Lardy, Ed. ix + 102 pp. John Wiley and Sons, Inc., New York 16, N. Y., 1960. Price: $5.25.

As the title indicates, this manuscript is devoted to the presentation of the methods of preparation and identification of various biochemical substances. Each procedure listed has been checked by scientists in other laboratories to ensure the ability of others to follow the same procedures.

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E. E. VOGIN

Pharmacology in Nursing. Eighth Edition. By Elsie E. Krug. 805 pp. C. V. Mosley Co., 1960. Price: $6.00.

This eighth edition of a widely accepted textbook represents considerable revision to include changes present in the recent editions of the *Pharmacopeia of the United States* (1960), the *British Pharmacopoeia* (1958), and the *National Formulary* (1960).

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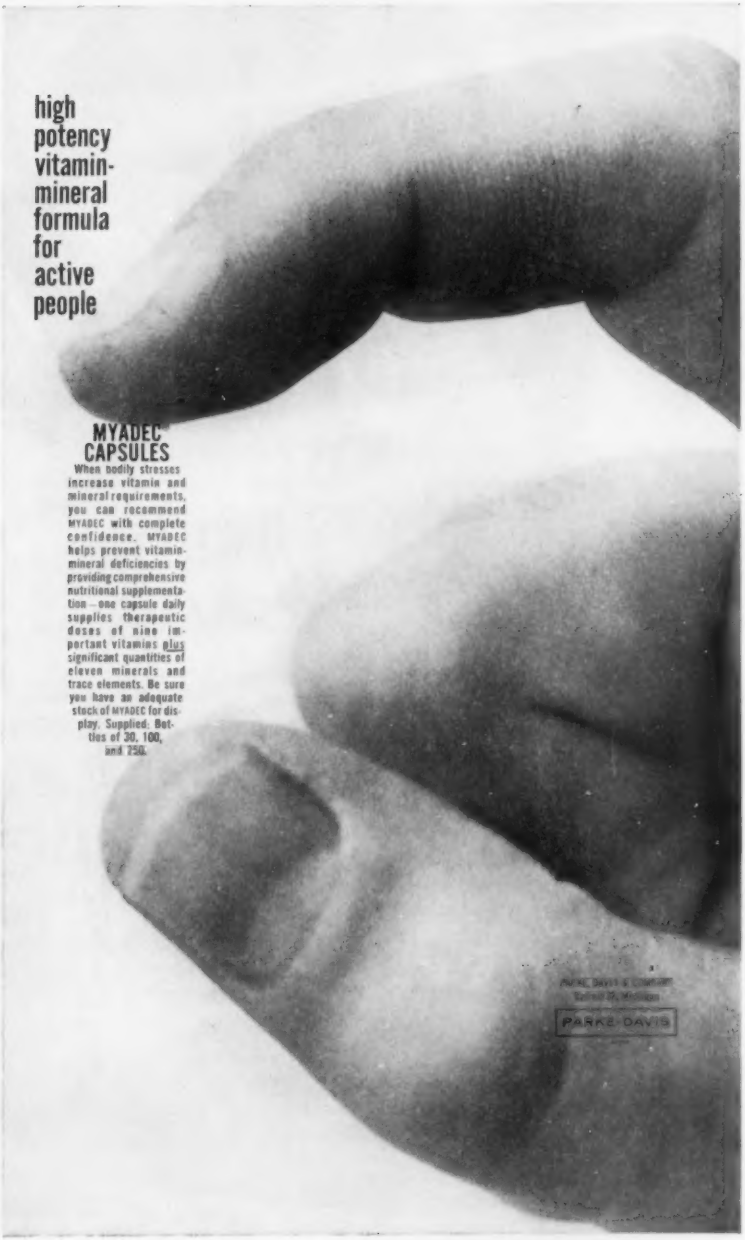

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